

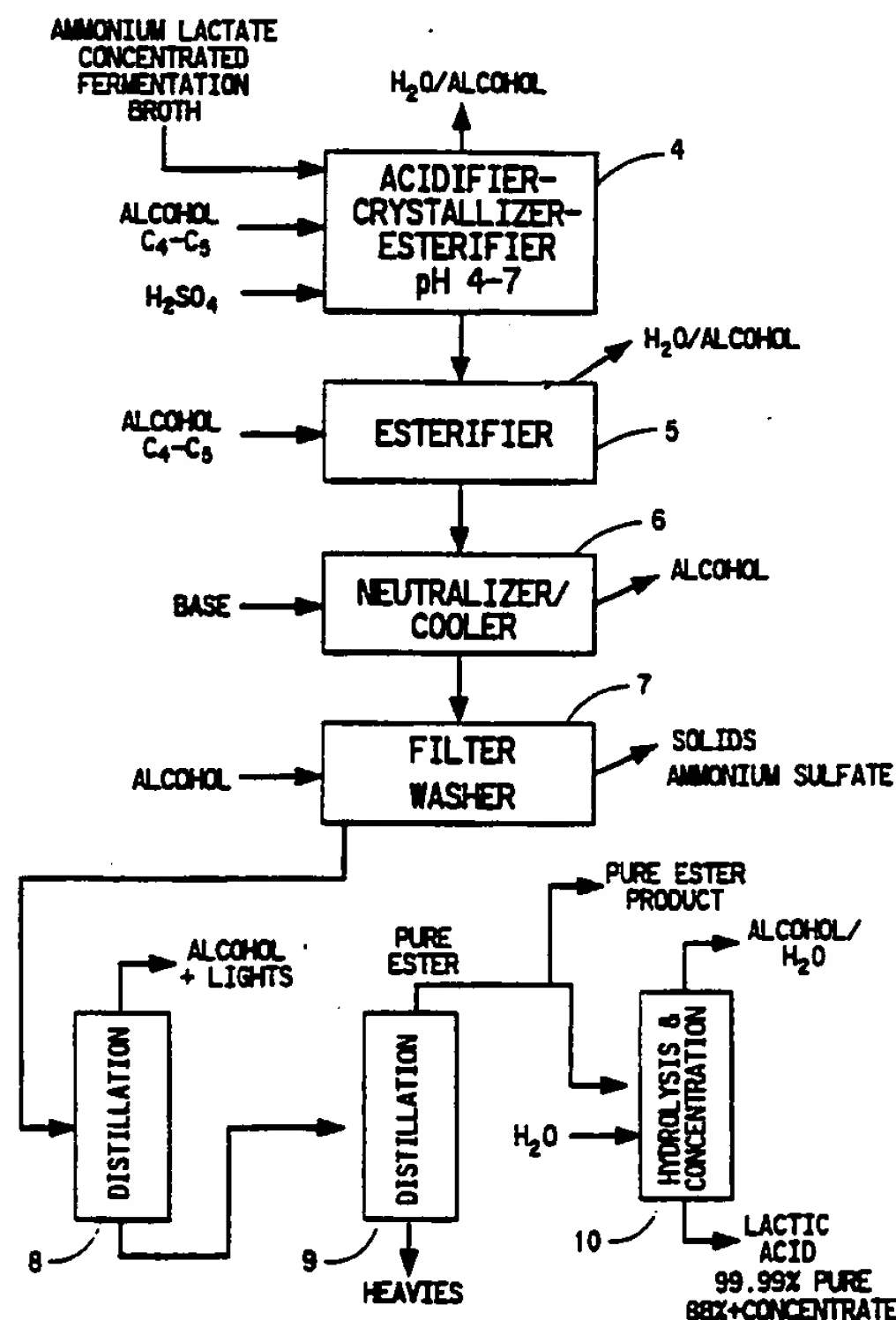


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C12P 7/56, C07C 67/54, 69/68	A1	(11) International Publication Number: WO 93/00440 (43) International Publication Date: 7 January 1993 (07.01.93)
(21) International Application Number: PCT/US92/04192 (22) International Filing Date: 27 May 1992 (27.05.92) (30) Priority data: 718,542 20 June 1991 (20.06.91) US (71) Applicant: E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US). (72) Inventors: COCKREM, Michael, Charles, Milner ; 224 Westmorland Boulevard, Madison, WI 53705 (US). JOHNSON, Pride, Douglas ; 828 Chaplin Court, Plymouth, WI 53073 (US). (74) Agents: KRUKIEL, Charles, E. et al.; E.I. du Pont de Nemours and Company, Legal/Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AU, CA, FI, JP, KR, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published <i>With international search report.</i>

(54) Title: RECOVERY OF LACTATE ESTERS AND LACTIC ACID FROM FERMENTATION BROTH**(57) Abstract**

The production of high purity lactate ester or lactic acid from a concentrated fermentation broth by continuous acidification in the presence of an alcohol diluent with sequential or simultaneous esterification, distillation off of high purity ester, and, if desired, hydrolysis of the ester to high purity lactic acid.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

TITLERECOVERY OF LACTATE ESTERS AND LACTIC ACID
FROM FERMENTATION BROTH

5

FIELD OF THE INVENTION

This invention relates to the production of high purity lactate ester or lactic acid from fermentation broth.

10

BACKGROUND OF THE INVENTIONProduction of Lactic Acid by Fermentation

Lactic acid can be produced by the continuous or batch fermentation of sugars or other biomass streams such as hydrolized starch, sulfite waste liquor or cheese whey.

For a rapid and economic fermentation, the pH of the broth is usually maintained in the range of 5.2-6.8 by either (a) continuously removing lactic acid such as by extraction, or membranes, or ion exchange, or electrodialysis, or (b) continuously adding a base such as aqueous ammonia, calcium carbonate, calcium hydroxide, or sodium hydroxide, or (c) starting the fermentation with a growth medium with substantial buffering capacity, such as a calcium carbonate slurry.

In each case, the fermentation broth may or may not have the fermentation microorganisms or enzyme slurry removed.

30

Figure 1 illustrates one method of preparing a concentrated fermentation broth. Steps (1) to (3) are not part of the present invention, but are included for illustrative purposes only. Fermentation takes place in unit 1 where nutrients and whey/permeate are fermented at about 40°C, and a pH of about 5.6. The stream from the fermentation unit 1

35

-2-

containing about 10-12% lactate salt optionally is filtered by membrane filter or centrifuge 2, which removes the biomass and any other solids. The aqueous stream leaving the filter contains about 95 g/l of lactate salt and 2 g/l of succinate salt, 1 g/l of acetate salt and other impurities.

This stream from filter 2 goes to an evaporator 3, where excess water is removed to give a concentrated broth containing 10-40% water, the balance being primarily the lactate salt of the base used for fermentation pH control.

The Nature of Lactic Acid

Lactic acid of commerce is typically a nominal 88% lactic acid solution and 12% water. In reality, this is an equilibrium or non-equilibrium mixture of lactic acid monomers, dimers, trimers and other lactic polymers of low molecular weight, plus water.

Hereinafter, reference to "lactic acid" also includes mixtures of lactic acid with lactic acid dimers, trimers, low molecular weight polymers and water.

"Heat stable" lactic acid refers to acid which does not readily decolorize upon heating at 180°C. However, organic acid impurities such as acetic acid and some salt impurities such as calcium salts do not cause discoloration at 180°C. Thus, heat stable lactic acid need not be and is often not chemically pure. The term is a lower purity designation.

Lactic acid may exist as either of two stereochemical enantiomers or so-called "optical isomers", D-(+)-lactic acid and L-(-)-lactic acid. A mixture of 99% "optical" purity is either (a) 99% D and 1% L, or (b) 1% D and 99% L.

5 A mixture of molecules of both forms is called a racemic mixture, or DL-lactic acid. The optical purity refers to the optical purity of the mixture of all forms of lactate, lactic acid, monomers, dimers, etc.

Salts of lactic acid also retain optical purity, as do compounds produced by chemical reaction of lactic acid, depending on the reaction and purification sequence.

10 The optical purity differs from the chemical purity. Hereinafter reference to purification of lactic acid means removal of non-lactic acid, non-water components. Some separation sequences will produce a chemically purified product which is
15 racemic, while others will produce a chemically purified product which also has high optical purity.

Traditional Processes for Lactic Acid Purification

20 Direct distillation of lactic acid from a crude acidified fermentation broth at normal temperature and pressure for recovery of the lactic acid has not been acceptable because lactic acid forms high boiling internal esters as dimers and polymers during the distillation, resulting in poor yields of
25 lactic acid (Smith and Claborn, JACS 61, 2727, 1939).

Repeated vacuum steam distillation has been used to produce monomeric lactic acid in high yield from a purified monomer-dimer-trimer mixture. However, this method requires a partially purified
30 lactic acid to start with, entails expensive equipment, and is not effective in removing impurities (Leonard et al., IEC 40 57, 1948).

Fractional distillation at high vacuum and low temperature is too expensive for practical
35 commercial operation.

Both the D and L forms of lactic acid can only be crystallized with great difficulty and in low yields. (Atkinson and Mavitnua, Biotech Bioeng. Handbook, Nature Press, 1983, pg. 1047).

5 These difficulties with simple processes lead to the traditional complex processes for producing lactic acid. For example, the fermentation pH is controlled by addition of calcium hydroxide or calcium carbonate. The resulting calcium lactate
10 solution at pH 5-7 is then purified by a complex sequence of operations including one or several of each of the following steps in a variety of possible sequences involving both lactate salt streams and lactic acid streams; evaporation, acidification with
15 sulfuric acid, filtration, washing of filtrate cake with cold water or with fresh broth, activated carbon bleaching, hydrogen sulfide metal precipitation, rotary vacuum filtration, and filter press filtration.

 Specifically, Inskeep et al., IEC 44, pp.
20 1955-1966 (1952) report a process involving 7 filtration steps, one decanter, 7 stirred tanks, calcium lactate evaporators, and lactic acid evaporators. This process does not even produce a lactic acid product of high purity, rather it produces a crude 50%
25 edible grade lactic acid and a 44% technical grade lactic acid.

 The high solubility of calcium lactate in water makes losses in wash water and mother liquor a significant problem for purification of lactic acid
30 via calcium lactate precipitation. Furthermore, to obtain high purity material this purification sequence must be followed by further purification steps.

Other Processes to Purify Lactic Acid

Other processes which have been tried to produce high purity lactic acid include multiple recrystallization of salts such as calcium lactate; solvent extraction using ether or a long chain amine; purification by ion exchange chromatography; electro dialysis; and separation and hydrolysis of lactic esters. If an alcohol is used as an extracting agent, extraction can be simultaneous or sequential to esterification.

Although the recrystallization technique can be successfully used to prepare a pure salt, say calcium lactate, this is expensive and the product must then be acidified such as with sulfuric acid to prepare the lactic acid.

Solvent extraction using ether requires very large volumes of ether. Any solvent which has high enough capacity for lactic acid to be economic, such as amyl alcohol or a tertiary amine, will also co-extract some water, salts and other organic acids. Thus, extraction alone does not economically produce a product of high enough purity.

Recently electro dialysis has been proposed for purification of lactic acid (Colon, PhD thesis, 1986). Currently this process has two disadvantages: high cost and a product of intermediate purity.

The literature frequently mentions that high purity lactic acid can be prepared by forming an ester, purifying the ester by distillation or extraction, and then converting the ester back to lactic acid. (Atkinson and Mavituna, Biotech Bioeng Handbook, Nature Press (1983), p. 1047.) Many of the procedures reported in the literature concern the esterification of partially purified lactic acid to form a heat stable lactic acid product, and do not

-6-

adequately address the needs for making a product of high chemical purity from a crude broth. Hereinafter, in the ester formation purification route the question of which alcohol is optimal for the complete process appears not to have been addressed prior

In lactic acid purification it is known that lactic acid can be reacted with high excesses of methanol to produce methyl lactate, with methanol and water being drawn overhead to drive the reaction.

An alternate method using methanol as the esterifying alcohol involves removing the ester continuously from the pot to drive the reaction. The scheme involves bubbling excess hot alcohol, such as methanol vapor, through the lactic acid solution at a temperature above the alcohol boiling point, whereby the lactate ester produced is removed with the alcohol vapors and water (Filachione and Fisher, IEC 38, 228 (1946)). Approximately 9 moles of methanol are required to remove one mole of lactic acid from an 82% solution. Dramatically larger quantities of methanol are required for more dilute lactic acid feed solutions. This may be acceptable if a highly concentrated pure lactic acid feed solution is used. However, the disadvantage of this is that there is little liquid alcohol or liquid ester present in the reaction broth. This means that the broth becomes a thick residue of impurities and partially reacted material, limited the yield in a given cycle.

The composition of matter of 1-butyl lactate is and its preparation are disclosed in Gabriel et al. U.S. Patent 1,668,806 (1928). They prepared 1-butyl lactate by dehydrating 70% lactic acid with excess 1-butanol at 117°C, followed by addition of HCl catalyst, followed by refluxing and esterification with addition excess 1-butanol and drawing a 1-butanol

water azeotrope overhead. Nakanishi and Tsuda
(Japanese Patent JP 46/30176 [71/30176]) consider
production of 1-butyl lactate by extraction of an
acidified crude fermentation broth with 1-butanol,
5 followed by esterification of the extract phase. BASF
(EP 159-285) considers production of isobutyl lactate
by extraction of an acidified crude fermentation broth
with isobutanol, followed by esterification of the
extract phase, which was then distilled in vacuum
10 80°C/25 mbar to give a purified isobutyl lactate.

Kaplan (PhD Thesis, 1966) suggests that
1-butanol is preferable to methanol and ethanol for
esterification. The use of methanol and ethanol in
the esterification entails high alcohol to water
15 ratios, and costly fractionating equipment for
separating the alcohol, water and ester. The relative
immiscibility of 1-butyl alcohol with water renders it
preferably to the infinitely soluble ethyl and methyl
alcohols for esterification when azeotropic
20 distillation is used for completion of the reaction.

Kaplan proposes a process with a
distillation column for continuous esterification of a
nearly pure 50% food grade lactic acid. The overheads
are condensed and the butanol phase is refluxed to the
25 esterification column. There is no purge for light
organics such as butyl-acetate, and thus his process
will not make high purity product. The esterified
column bottoms are fed directly to a second column
where the butyl-lactate is separated from the
30 high-boiling impurities. The purified butyl-lactate
is steam hydrolyzed with an HCl catalyst. The HCl
will cause dramatic corrosion problems in the lactic
acid hydrolysis column, and will contaminate the
product with chloride ions. Kaplan does not consider
35 higher alcohols.

Smith and Claborn (IEC 32,262, 1940), note
"It is more difficult to obtain a high yield of ester
with methyl or isopropyl alcohol than it is with a
long chain alcohol such as butyl, amyl, cetyl, lauryl
5 and stearyl."

It is known that water removal can be
carried out by using a higher alcohol that is
sufficiently high boiling and slightly soluble in
water (Filachione et al., JACS 70,526 (1948)).
10 1-Pentanol and higher alcohols have been esterified
this way (Smith et al., IEC 32,692 (1940)). Grutein
et al. (U.S. Patent 1,160,595) also suggest that the
higher molecular weight alcohols are preferable.

Azeotropic removal is necessary to remove
15 the last traces of water economically from the
esterification. Benzene has been used as an
azeotropic entraining agent to remove water from a
methanol-water-lactic acid reaction broth for the
production of methyl lactate. The benzene-water
20 overhead stream is condensed and the benzene and water
phases separated. This process has the disadvantage
of adding complexity due to the additional component.

SUMMARY OF THE INVENTION

25 This invention relates to a process for
recovery of high purity lactate ester or lactic acid
from fermentation broth containing ammonium lactate or
other basic salt of lactic acid; acidifying in the
presence of an alcohol of 4-5 carbon atoms as a
30 diluent using continuous addition of sulfuric acid or
other strong acid and crystallizing to precipitate out
some or all of the basic salt of the strong acid;
simultaneously or sequentially removing water from the
acidified material as an alcohol water azeotrope
35 overhead while also esterifying the lactic acid with

the alcohol of 4-5 carbon atoms to form impure lactate ester; removing the crystals formed; distilling the lactate ester to remove impurities, residual water and excess butanol to yield high purity lactate ester; and
5 hydrolyzing, if desired, the ester while removing alcohol and water to form high purity lactic acid.

Purities in excess of 99.5% lactic acid at concentrations approaching 90% lactic acid are obtainable, with retention of the optical purity of
10 the feed material.

This invention is applicable to the purification of any crude fermentation broth containing an equilibrium mixture of salts of lactic acid and free acid itself, regardless of the exact sequence of steps
15 used to perform the fermentation and prepare the crude broth. In particular, our invention relates to the use of ammonium as the dominant salt.

One aspect of the invention which distinguishes it from earlier work is that it produces a
20 lactic acid or lactate ester product that is both of high optical purity and high chemical purity. It can also be used to produce lactic acid or lactate ester product that is optically racemic and of high chemical purity.

25

DETAILS OF THE INVENTION

This invention relates to the process for recovery of lactic ester or lactic acid from a crude fermentation broth containing primarily the salt of a
30 strong or weak base with lactic acid, along with other components.

The process comprises the steps of:

(1) acidifying in the presence of an alcohol of 4-5 carbon atoms as a diluent while continuously
35 adding sulfuric acid or other strong acid, and

-10-

- crystallizing to precipitate out some or all of the basic salt of the strong acid;
- (2) simultaneously or sequentially with step (1) removing water from the acidified material as an alcohol water azeotrope while also esterifying the lactic acid with an alcohol of 4-5 carbon atoms to form impure lactate ester, which step may be undertaken in one vessel or several vessels in series;
- (3) removing the crystals formed before or after neutralization of any excess acid, with or without cooling;
- (4) distilling the lactate ester to remove impurities, residual water and excess alcohol to yield high purity lactate ester; and
- (5) if desired, hydrolyzing the ester while removing alcohol and water to form high purity lactic acid.

It has been found that high yields of very high purity lactic ester or lactic acid can be produced economically by using a high boiling alcohol of 4-5 carbon atoms as the ester forming alcohol. This avoids the formation of dimer and polymer products and the hydrolysis or other reaction of the ester in the distillation step, thereby giving yields in the 85-98% range of 99+% purity lactate in lactic acid. By this technique optical purity of the lactic acid is retained as produced in fermentation. Virtually no racemization results.

This purification of lactic acid by the high-boiling alcohol ester route to obtain high yields of high purity lactate ester or lactic acid and efficient alcohol recovery requires the following:

(1) efficient esterification with high yield and effective water removal;

-11-

- (2) high yield distillation to separate out both light and heavy impurities with minimal loss of lactate ester;
- (3) efficient hydrolysis to remove substantially all alcohol, with high conversion to lactic acid; and
- (4) recovery of the alcohol by the formation of a heterogeneous alcohol/water azeotrope that can be separated to yield water-free alcohol.

The process of this invention is a low cost process for making very high purity product that has retained its optical purity. The steps that make this possible are:

- (1) the ability to feed concentrated fermentation broth containing primarily a basic salt of lactic acid in aqueous solution, with or without removal of the biomass, directly to recovery;
- (2) continuous acidification with strong acid in the presence of an alcohol diluent, which yields crystals of an appropriate size for simple removal by filtration and effective washing; and
- (3) the use of a high-boiling alcohol esterification agent that is optimal for the steps of production of the ester, distillation of the ester, and, also, if necessary, hydrolysis of the ester.

A main feature of this invention is that a high purity lactate ester or lactic acid can be produced with the minimum number of process steps. Each process step can accommodate a wide variety of impurities, as is usually encountered in fermentation processes. No pretreatment is needed for the broth, and by this process the product is freed of all impurities including salts, organic acids, sugars, odors and cell residues. The process can be run either continuously or batchwise, and the optimum alcohols have been identified which maximize yield in the distillation and esterification steps with the

minimum costs for esterification and distillation equipment.

Also, in the preferred form of the invention, with ammonium lactate as the main fermentation product and sulfuric acid as the acidify acid, the use of continuous stirring during acidification leads to the growth of large crystals which are far more easily removed and washed than the traditional calcium sulfate crystals.

The only waste from this process is the crystal precipitate which contains process impurities, still bottoms from the distillation step and water containing other fermentation impurities.

The preferred 1-butanol (n-butanol) ester is highly efficient in the hydrolysis step. Since it has a boiling point substantially lower than that of lactic acid, virtually all ester can be removed from residual lactic acid product, and n-butanol is readily removed from the reaction mass to drive the hydrolysis to substantially 100% completion. The n-butanol can readily be recovered and recycled in this process because it forms a heterogeneous azeotrope with water.

Thus, it has been determined that for optimum recovery of lactic acid from fermentation broth while retaining its optical purity, the use of n-butanol as the esterifying agent produces optimal results of high yield, high purity and optically unaltered lactic acid product. N-butanol has the ideal properties of (1) a boiling point at least 15°C above the boiling point of water and at least 20°C lower than the boiling point of lactic acid; (2) substantial immiscibility in water; and (3) the ability to form a heterogeneous azeotrope with water.

Another important facet of the present invention is the choice of base for neutralization of

the lactic acid in the fermentation broth. This significantly affects the operation and economics of the subsequent lactic acid purification and recovery. Specifically in the preferred form of the present invention ammonium hydroxide is used to give a fermentation broth of pH 5 to 7. And, importantly, the ammonium sulfate salt produced can be crystallized into a readily filterable form.

Also in the preferred practice of the present invention, draft tube baffled crystallizers instead of stirred tanks are used to produce the lactic acid ester giving the desired easily filterable ammonium sulfate crystals.

The economy of this invention is related to the cost of recovery of dry alcohol for recycle to the esterification. This is related to the amount of water removed per unit of alcohol taken overhead and to the split of water between the heavy and light phases of the heterogeneous azeotrope. This can be seen in Table 1, which shows the "water efficiency", the weight of water passing into the heavy phase per weight of water in the alcohol phase. This shows that the condensed azeotrope of 1-butanol with water can be split into a heavy and light phase, where the heavy phase has 2.1 times the amount of water as the light phase. This number must be high for economical water removal because the light overhead phase contains 20% water that needs to be dried in a separate distillation column before reflux to the esterifier if high rates and good yield are to be obtained. The heavy phase contains 70,000 ppm alcohol which is stripped before that water can be reused in the fermentation or discarded. Of the butanols, 1-butanol is the most efficient for water removal. As the Table shows the higher the alcohol, the more efficient it is for water removal. However, physical properties such as

-14-

the high viscosity of very high molecular weight alcohols limit their use.

TABLE 1

5		Alcohol Normal Boiling Point °C	Overhead Vapor Azeotrope Molar Efficiency mol water mol alcohol	Condensed Heterogenous Phase Water Efficiency g water lower g water upper
10	<u>Homogeneous Azeotropes</u>			
	ethanol	78.5	.1	
	iso-propanol (2-propanol)	82.3	.5	
	tert-butanol	82.8	.6	
15	(2-me-2-propanol)			
	propanol	97.2	1.3	
	<u>Heterogeneous Azeotropes</u>			
	iso-butanol	108.4	1.8	1.3
20	(2-methyl-1-propanol)			
	(tert amyl)	102.3	1.8	
	2-butanol(sec)	99.5	1.9	
	2-methyl-1-butanol	128.0	2.3	
	3-methyl-2-butanol	112.9	2.4	
25	3-pentanol	115.6	2.6	3.4
	2-pentanol	119.3	2.8	
	1-butanol	117.7	3.3	2.1
	iso-pentanol (iso-amyl)	132.0	6.0	
30	pentanol (n-amyl)	138.0	6.0	
	c-pentanol	140.9	6.8	
	2-ethyl-1-butanol	148.9	6.8	20.1
	hexanol	158.0	11.6	21.6
	1-octanol	195.0	65.0	
35	2-butyl octanol	253.4	403.0	2939
	decanol	283	greater than	3000

Also studied were the efficiency of ester distillation for purification and ester hydrolysis to determine if indeed these higher alcohols are optimal. In contrast to much earlier work, it was found that to
5 prepare high purity esters it is necessary to carefully distill off "light" impurities with boiling points less than that of the ester, and then distill the ester away from "heavy" impurities with boiling points greater than that of the ester. Thus there are
10 three reasons against using higher alcohols in the distillation step.

Firstly, lactate esters can decompose and transesterify and can also react at the free hydroxy group on the lactate part of the ester. For example,
15 two molecules of octyl-lactate can react to form octyl-lactyl-lactate plus octyl alcohol. This reaction is driven by the elimination of the octyl alcohol overhead. The octyl-lactyl-lactate is then a yield loss in the distillation of octyl-lactate from
20 light or heavy impurities. To minimize this reaction, temperatures lower than 150-180°C must be used, depending on contact time.

Furthermore, the racemization (loss of purity) is less at lower temperatures. To obtain
25 distillation at these low temperatures, very low pressures must be used for higher alcohol esters, and the distillation column size becomes prohibitively expensive.

Secondly, some unreacted lactic acid remains
30 in the esterification pot. This will distill at a boiling point close to that of butyl lactate, or less than that of higher esters. Thus, in trying to distill higher esters, lactic acid will distill. Unfortunately, lactic acid will also dehydrate under
35 such conditions of temperature and pressure and a polymer will form. This will have high viscosity and

will elevate the boiling point of the distillation bottoms further.

Therefore, lower boiling esters are favored in the distillation process.

5 In fact, it would seem obvious that methyl lactate would be the preferred ester for the distillation step since the temperature at which methyl-lactate boils at atmospheric pressure is only 143°C. However, it is not in fact the optimum, because as the
10 methyl-lactate distillation is started first methanol distills overhead, then water, then methyl-lactate, then lactic acid. Thus, there is a hot solution of water and ester present in the distillation tower which brings about hydrolysis of the ester. The rate
15 of hydrolysis in such operations can be significant (Colon et al., J. ACS., 76,6074 (1953)).

Consider Japanese Patent JP 62/26249 (87/26249) for the production of C₁-C₆ lactate esters by refluxing crude lactic acid with alcohol in aqueous
20 sulfuric acid (pH 2.3), followed by pH adjustment to 6.0 to 8.5 with aqueous sodium hydroxide, and distillation of the ester with benzene as an entraining agent. Here the benzene is required in the distillation of the methyl-lactate to ensure good
25 yields in that distillation step. We have found that by selecting the optimal alcohol for esterification, we can eliminate the added complexity of using benzene in the ester distillation.

Yield in the distillation of the ester is
30 affected by two factors, namely, hydrolysis of the ester back into acid due to residual water, and formation of dimer and polymer products by reactions between ester, unreacted acid and impurities. Distillation yield losses due to hydrolysis are
35 lessened by using an alcohol with a boiling point greater than that of water.

-17-

TABLE 2

		<u>Normal Boiling Points</u>	
	<u>Lactate Ester of</u>	<u>Alcohol</u> <u>°C</u>	<u>Lactate</u> <u>Ester</u> <u>°C</u>
5	ethanol	78.5	154
	iso-propanol (2-propanol)	82.3	167
	1-propanol	97.2	169
	tert-butanol	82.8	>175
	(2-methyl-2-propanol)		
10	2-butanol (sec-butanol)	99.5	>180
	iso-butanol	108.4	182
	(2-methyl-1-propanol)		
	1-butanol	117.7	187
	2-methyl-2-butanol	102.3	>185
15	(tert amyl)		
	(dl)-3-methyl-2-butanol	112.9	>190
	3-pentanol (sec-amyl)	116.1	>195
	2-pentanol	118.9	>195
	(1)-2-methyl-1-butanol	129.0	198
20	(iso-amyl)		
	pentanol (n-amyl)	138.0	206
	c-pentanol	140.9	>200
	2-ethyl-1-butanol	146.3	
	hexanol	158.0	221
25	1-octanol	195.0	256
	2-butyl octanol	253.4	
	decyl		283
	dodecyl		310
	tetradecyl		335
30			
35			

TABLE 3

Determination of the Optimum Alcohol
for Ester Distillation

	Alcohol Type	<u>Ethanol</u>	<u>Butanol</u>	<u>Hexanol</u>	<u>Octanol</u>
5	Alcohol molecular weight	46	74	102	130
	Alcohol NBP	79	117	158	195
	Lactate Ester MW	118	146	174	202
	Ester NBP	154	187	221	256
10	Pressure for 119°C overhead	251.19	74.99	21.88	3.80
	Density at 119°C (lb/ft 3)	.0756	.0279	.0097	.0020
	Vapor Flux for 1000 lb/hr LA in lb/hr of ester	1711	2078	2456	2844
15	D min for f - 0.50 feet	2.19	1.97	4.20	6.75
	= sqrt(4/pi. flux/sqrt dens. 1/f) (units of feet-sec-lb)				
	Relative Column Diameter	1.00	1.41	2.00	3.21
20					

These calculations assume that the overhead condenser temperature is fixed at 119°C, and that this allows the bottoms temperature to be kept low enough to minimize decomposition while still obtaining adequate yield of ester.

Thus, it can be seen that for the purification of lactate esters by distillation, alcohols with boiling points greater than that of water which form heterogeneous azeotropes with water and have the lowest lactate ester boiling points, at least less than 200°C at 760 mm Hg, are the preferred alcohols.

These preferred alcohols contain 4 or 5 carbon atoms and so include: iso-butanol (2-methyl-1-propanol), 1-butanol, 2-methyl-2-butanol (tert amyl alcohol), (DL, L or D)-3-methyl-2-butanol, 3-pentanol

(sec-amyl alcohol), 2-pentanol, and ((DL, L or D)-2-methyl-1-butanol (iso-amyl alcohol). Note that two optical isomers (D-form and L-form) exist for each of the alcohols 3-methyl-2-butanol and 2-methyl-1-butanol, and that a mixed form DL can also be used.

Of these alcohols, 2-pentanol has the greatest water efficiency and iso-butanol the least. However, 1-butanol and iso-butanol are more readily available commercially in good purity. Iso-butanol has a lower water efficiency than 1-butanol, and is less economical. Thus, 1-butanol is the preferred alcohol for lactate ester purification by esterification in the process of the present invention.

Other hexanols can be used but require much larger distillation columns due to the need for lower pressure to maintain the lower temperature required for avoiding lactate decomposition. Higher alcohols are even less favorable.

Thus, it has been found that the optimum alcohols for purification of lactate ester by distillation are those containing 4 or 5 carbon atoms, which are optimum for the following reasons: for retention of optical purity, for minimization of equipment size, for minimization of energy requirements, and for maximization of distillation yield with minimization of side reactions.

As aforementioned, in the present process high purity lactic acid is produced by hydrolysis with water of the high purity lactate ester to produce lactic acid plus the alcohol, and then stripping the alcohol and any unreacted ester from the lactic acid-water product. To obtain low residual levels of the ester, high conversion of the ester driven by removal of the alcohol is needed, followed by economical removal of any residual ester such as by

steam stripping. Here the more volatile the alcohol and ester are, the easier it is to remove them from the reaction broth. However, the lower molecular weight lactate esters form azeotropes with water which are rich in the ester, which makes them more difficult to hydrolyze. There is thus an optimum ester for the hydrolysis step alone, one that does not form an ester-water azeotrope which is rich in the ester, yet one that the alcohol formed is easily stripped.

10 Pentyl and butyl lactates are favored, propyl-lactates, ethyl-lactate and methyl-lactate also being suitable.

Thus, the optimum esters as intermediates for lactic acid production will require a balance between needs for ester formation, ester purification and ester hydrolysis.

15

Additionally, the present invention encompasses an economical procedure to operate the esterification reactor or reactors which substantially reduces the number of equipment pieces, the process complexity and increases the yield of ester.

20

The calcium salts formed in the acidification of calcium lactate broth with sulfuric acid are often fine crystals that are difficult to filter (Inskeep et al., previously cited). There is no mention in the literature of the design of correct crystallization equipment nor the relationship of effective crystal washing to good yield, nor the selection of the appropriate filter for this task. As well as selecting the optimal alcohols, this invention pertains to the selection of correct equipment for these steps.

25

30

It has been found that the acidification of the basic salt of ammonium lactate must be undertaken in a continuous or semicontinuous manner to grow

35

crystals which are the correct size for easy filtration and high efficiency washing.

Any suitably stirred vessel can be fed simultaneously with a concentrated fermentation broth containing a basic salt of lactic acid plus other impurities, a strong acid and an alcohol. The location of the feeds should preferably be below the liquid surface. Crystals of the basic salt of the strong acid are formed, and the lactic acid and alcohol react to form the lactate ester. The stirred reactor is heated to the boiling point and the alcohol-water azeotrope continuously removed overhead driving the reaction to the ester and also precipitating more crystals as the water is removed. The liquid product is continuously drawn from the reactor, and may pass directly to a suitable filter to remove the solids, or to further reactors or cooling and neutralization prior to filtration. The key to this equipment simplification is that the acidification and esterification can be completed simultaneously in a single reactor, or sequentially in a series of continuous reactors, in the presence of many of the crude materials present in the original fermentation broth. The crystal growth is aided in all cases by the presence of the alcohol as a diluent.

Furthermore, in the preferred form of this invention, it has been found that a fermentation broth predominantly composed of the ammonium salt of lactic acid when neutralized with sulfuric acid in the correct manner leads to crystals which are easily filtered and washed.

Figure 2 schematically shows the preferred practice of the present invention.

The crude fermentation broth containing primarily the salt of a strong or weak base with lactic acid, but also other components, for example,

as from Unit 3 in Figure 1, but also possibly from any other source, goes to the simultaneous acidification and crystallization Unit 4 where alcohol is added as a diluent and a strong acid such as sulfuric acid is added to a pH of about 1.5 to form lactic acid and the base salt of the strong acid, for example, ammonium sulfate. Esterification will occur in this vessel, and an alcohol water azeotrope may be taken overhead. The partially or fully esterified product from Unit 4 may optionally pass to Unit 5, which may be one or several reactors in series for further simultaneous esterification and crystal growth and water removal overhead as the water alcohol azeotrope.

The product from Unit 4 or Unit 5 then passes to Units 6 and 7. These Units may be in the illustrated order, or in reverse order with Unit 7 preceding Unit 6. The reaction broth is neutralized, cooled and the crystals removed by filtration. The crystals are washed with dry alcohol to increase yield. The wash alcohol may be recycled or passed to Unit 8 with the mother liquor.

In Unit 8 the alcohol and other light impurities are separated from the ester and heavy impurities, which pass to Unit 9 where the ester is distilled overhead under vacuum to separate it from the heavy impurities.

The pure ester product then may be optionally hydrolyzed with water to lactic acid in Unit 10, in the presence of an acid catalyst, which may be lactic acid under pressure or a catalyst bed containing strong acid ion exchange resin. Butanol is removed and the product stream is concentrated by the removal of water, yielding the final product stream consisting of 88% aqueous lactic acid of 99+% purity having the optical purity of the original fermentation lactic acid.

-23-

EXAMPLE 1

Six gallons of concentrated fermentation broth containing 59% ammonium lactate, 13% other salts and fermentation residues, and 28% water is charged to a 50-gallon glass lined reactor with a recurve three-blade agitator. Ten gallons of 1-butanol are added. The stirrer is started at 130 rpm such that the impellor tip speed is not excessive for crystal growth. Next 1.5 gallons of 98% sa is metered into the reactor continuously over the next 30 minutes. Crystals which are predominantly composed of ammonium sulfate but include some of the fermentation salts and other components grow in this time. The reactor is sampled and more sulfuric acid added until the pH is between 1.0 and 1.5.

The heat to the reactor is started and a 1-butanol-water azeotrope withdrawn overhead through a short column to a condenser. The condensed overhead phase separates into a light butanol rich and a heavy water rich phase. Reflux of the light phase is taken from a reverse dean and stark trap back to the column. Fresh dry 1-butanol is added to the pot to replace butanol which is removed overhead. The pot temperature is raised slowly to 115°C. As the water content of the pot drops, the overhead phase ceases to be two phases, and only a portion of the light butanol rich phase is returned to the column. As the water content of the pot drops, the crystals grow in size. In all, an additional 10 gallons of 1-butanol is added during the course of the reaction.

Upon completion of the reaction, the pot is cooled by drawing a vacuum of between 50 and 300 mm Hg on the condenser and receiver. Some reflux is maintained on the column. Considerable butanol is drawn off overhead. The residual material is a suspension of crystals in a solution which is

primarily butyl-lactate ester and 1-butanol, but contains some soluble organic and inorganic impurities, plus residual sulfuric acid and lactic acid. This mixture is then carefully neutralized to
5 pH 6.66 to 8.0 by the addition of anhydrous ammonia or other anhydrous base. Mixing is maintained. Slight additional crystal growth occurs.

The suspension is now filtered by draining the entire reactor pot contents into a 2.5 foot
10 diameter Buchner funnel with a woven gauze filter cloth. A vacuum is applied to the funnel and clarified liquor drawn into a receiver. The salts are easily washed using dry 1-butanol, which may be saved for use in the next batch of esterification or added
15 to the filtrate for distillation. Dry 1-butanol is particularly useful because it does not appreciably dissolve salt impurities.

The filtrate now contains butanol, butyl-lactate, light ester impurities such as
20 butyl-acetate, heavy ester impurities such as butyl-succinate, and other residual impurities. The filtrate is now distilled using any convenient available distillation sequence to produce a high purity butyl-lactate. The temperature of the final
25 heavy pot bottoms should not exceed 150-160°C to minimize yield loss. This requires that the distillation be conducted at pressures as low as 50 mm Hg.

30 EXAMPLE 2

Concentrated fermentation broth at pH 5.5 containing ammonium lactate and other acids and salts and impurities and 25% water at a flowrate of 6000
pounds per hour is continuously fed to a 10,000 gallon
35 draft-tube baffled stirred crystallizer with a steam heated jacket maintained at a constant temperature of

104°C. Simultaneously charged to the reactor is 12,000 pounds per hour of 1-butanol which may be recycled from other steps of the process after a suitable drying procedure. Simultaneously charged to the reactor is 2000 pounds per hour of concentrated sulfuric acid, controlled to maintain a pH in the reactor in the range of 1.0 to 1.6. All the addition points are located subsurface in a region of intense mixing, but with mixing velocities of less than 1500 ft/min. Simultaneously vapors containing butanol and water are drawn off overhead at a rate of 4000 pounds per hour and a liquid product is drawn off to maintain a constant level in the reactor. This reaction product is largely butyl-lactate and butanol, with suspended solid crystals which are predominantly ammonium sulfate. These crystals are of large size suitable for easy removal and effective washing in a filter or screening centrifuge.

20

EXAMPLE 3

The reaction product of Example 2 is fed to a second continuous draft tube baffled reactor in series with additional 1-butanol feed of 6000 pounds per hour and further takeoff of butanol and water overhead.

25

EXAMPLE 4

The product of either Example 2 or Example 3 is fed to a continuous stirred draft tube baffled flash vessel where butanol is drawn overhead continuously under vacuum at 100-300 mm Hg and dry ammonia gas fed subsurface to neutralize excess catalyst.

30

35

WHAT IS CLAIMED:

1. A process for recovering high purity lactate ester from a concentrated fermentation broth comprising the steps of:

- (1) simultaneously mixing a strong acid, an alcohol, and a concentrated fermentation broth which contains mainly basic salts of lactic acid, which react to form a crystal precipitate comprising basic salts of the strong acid and an impure lactate ester of the alcohol;
- (2) removing water from the mixture as a water/alcohol azeotrope which can be accomplished either sequentially or substantially simultaneously with step (1);
- (3) removing the crystal precipitate from the mixture; and
- (4) distilling the impure lactate ester to remove impurities, and recovering the high purity ester.

2. The process of Claim 1 wherein the alcohol contains from 4 to 5 carbon atoms.

3. The process of Claim 2 wherein the alcohol contains an alcohol selected from the group consisting of: iso-butanol (2-methyl-1-propanol), 1-butanol, 2-methyl-2-butanol (tert amyl alcohol), (DL, L or D)-3-methyl-2-butanol, 3-pentanol (sec-amyl alcohol), 2-pentanol, and (DL, L or D)-2-methyl-1-butanol (iso-amyl alcohol).

4. The processes of Claims 1 to 3 comprising the additional step of hydrolyzing the lactate ester to form high purity lactic acid.

5. The processes of Claims 1 to 4 wherein the concentrated fermentation broth contains at least 10% water and at least 45% ammonium lactate, and the strong acid is sulfuric acid.

6. The process of Claim 5 wherein ammonium sulfate is crystallized out in draft tube baffled crystallizers.

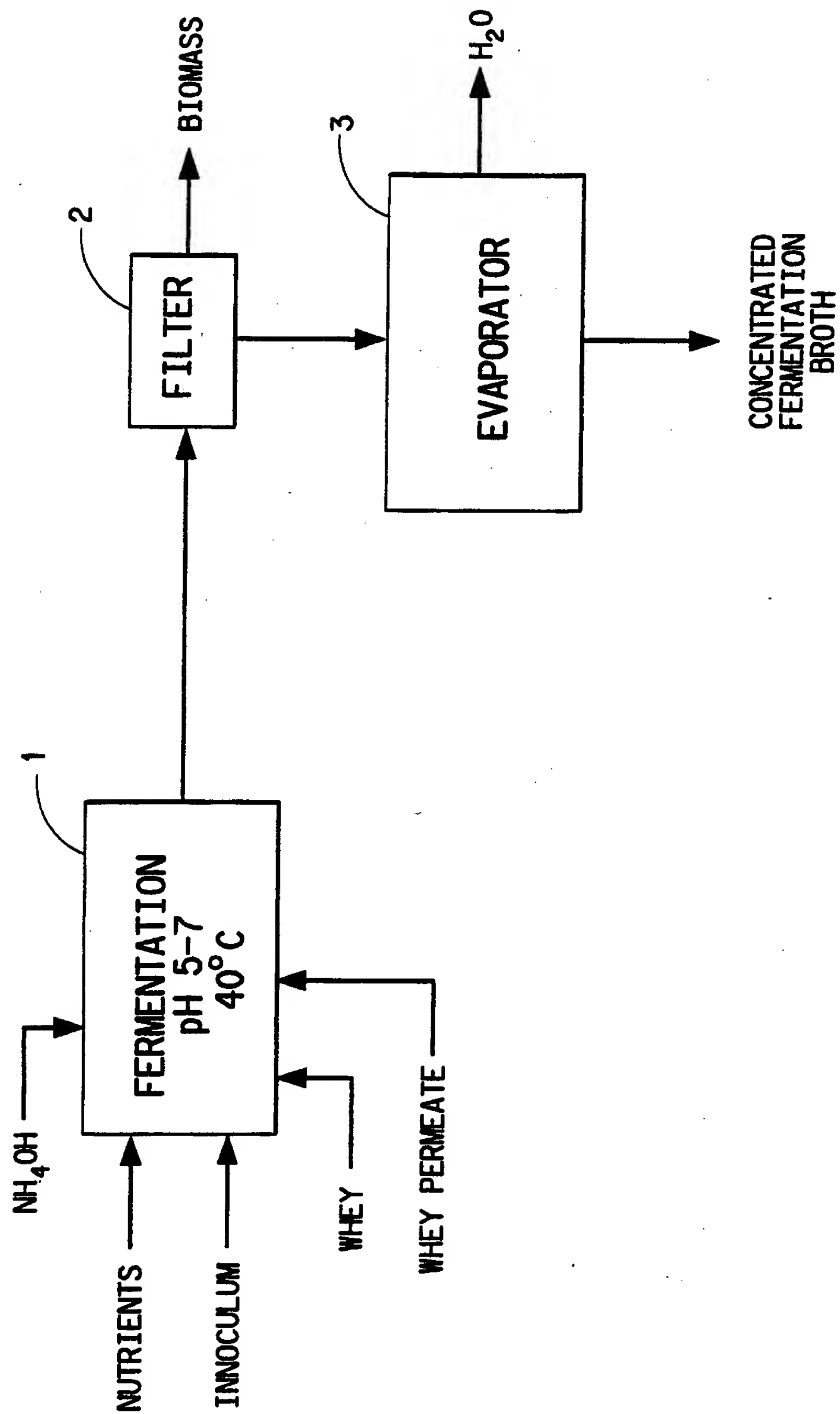
7. The processes of Claims 1 to 6 wherein the precipitated crystals are washed with dry alcohol.

8. The process of Claim 1 wherein the fermentation broth contains ammonium lactate of at least 98% optical purity and the lactate ester is at least 97% optically pure.

9. The process of Claim 4 wherein the lactic acid is at least 97% optically pure.

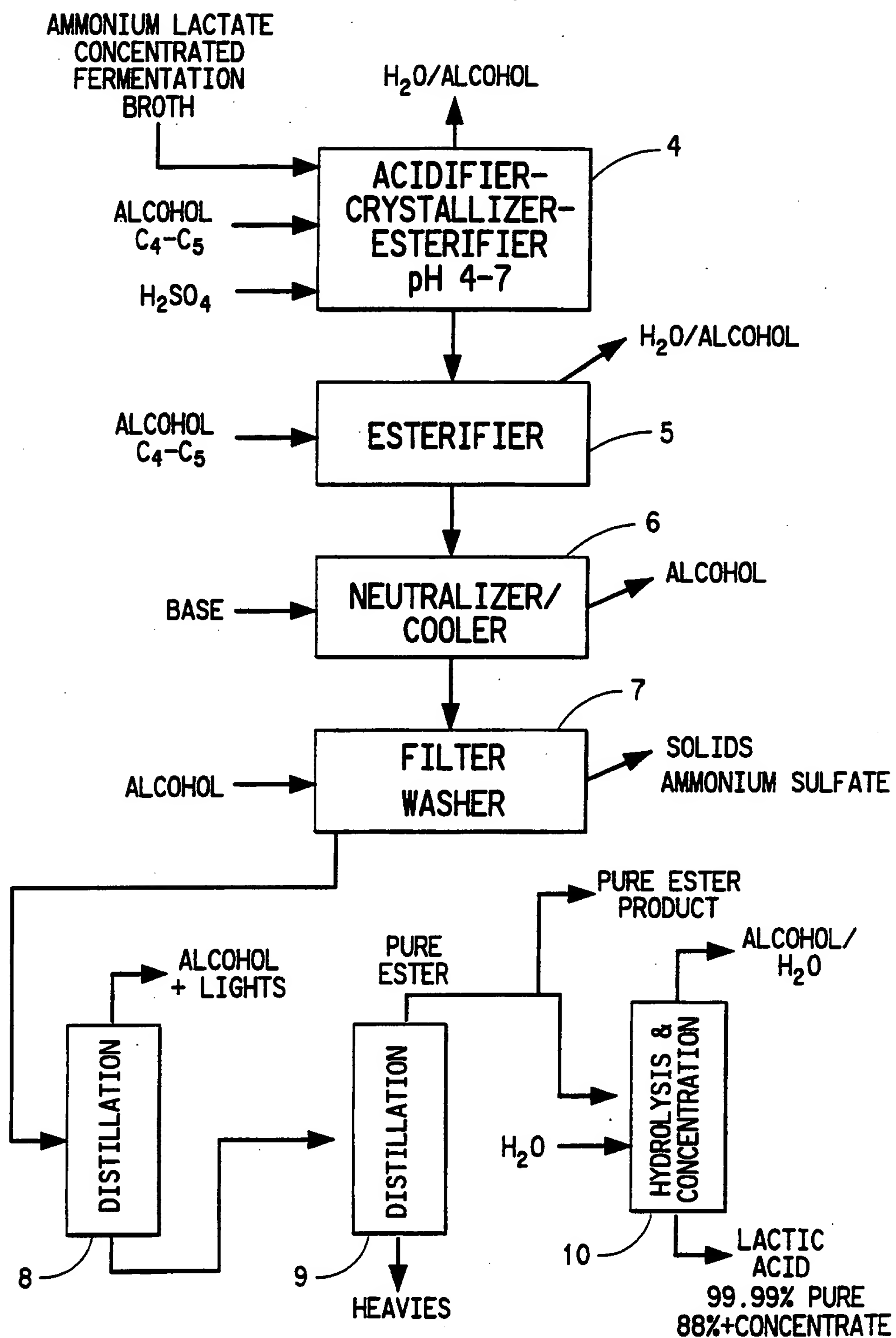
1/2

FIG. 1



2/2

FIG. 2



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04192

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C12P7/56; C07C67/54; C07C69/68		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C12P ; C07C	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claims No. ¹³
A	US,A,2 420 234 (EDWARD M. FILACHIONE ET AL.) 6 May 1947 see column 2, line 11 - line 34 see column 3, line 9 - line 22 see column 3, line 38 - column 5, line 65 ---	1-4
A	DD,A,206 373 (FRANKE, JOACHIM ET AL.) 25 January 1984 see page 3, paragraph 6 - page 5, paragraph 2 see page 6, paragraph 3 ---	1,4,5
A	US,A,166 806 (COMMERCIAL SOLVENTS CORPORATION) 8 May 1928 cited in the application ---	1-3
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
31 AUGUST 1992	11. 09. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	MONTERO LOPEZ B. 